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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket No. 2005D-0004, Federal Register January 26, 2005 (Volume 70, Number 16, Page 3714) "Draft Guidance for Industry on Nonclinical Safety Evaluation on Drug Combinations"**

Dear Sir or Madam:

We appreciate the Agency's efforts to enhance the nonclinical development of drug combinations through the preparation of this guidance by the Pharmacology Toxicology Coordinating Committee in the Center for Drug Evaluation and Research (CDER), and we also appreciate the opportunity to provide feedback.

Overall, we strongly support the development of this guidance document. Further, we believe that this guidance is very timely, as an increasing number of combination products are entering the development pathway. Below, we have provided specific comments outlining various points for clarification that relate to specific sections of this guidance.

Specific Comments:

**(a)**

**Section I, Introduction, Lines 19-21** ***"This guidance provides recommendations on nonclinical approaches to support the clinical study and approval of fixed-dose combination products (FDCs), co-packaged products, and adjunctive therapies. This document is only intended to delineate general guiding principles."***

The scope of this "general" guidance is clearly defined; however, it is not readily apparent whether the comments and recommendations found in this guidance are restricted to certain classes of molecules (*e.g.,* low molecular weight NCEs/NMEs). As the Agency is currently developing other draft guidances to specifically address certain types of combination products (*e.g.,* oncologic drug combinations), it is recommended that this current draft guidance incorporate wording to specifically include (or exclude)

biologics or biotechnology-derived products, or antisense oligonucleotides intended to treat chronic, non-oncology indications.

**(b)**

**Section IV, A. General Toxicology Studies, Lines 258-9** ***"If the two [new] drugs are proposed to be marketed together only, then it is possible that it may be sufficient to conduct toxicology studies only on the combination."***

Based on our interpretation of 21 CFR 300.50, the Sponsor is obliged to demonstrate in the clinic that the combination product is more efficacious than the individual components. For example, the recent approval of the Pegasys®/Copegus combination therapy for treatment of hepatitis C virus infection is consistent with such an approach, with data from the definitive clinical trial showing that the Pegasys® + Copegus cohort displayed a 53% sustained virologic response *vs.* 29% for the Pegasys® + placebo cohort. Thus, in order to support the proposed clinical use of the individual components in a trial(s) designed to meet the expectations of 21 CFR 300.50, we recommend that the Agency indicate in the guidance that Sponsors may rely on animal toxicology studies conducted with the fixed-ratio combination to support clinical trials with the individual agents.

**Clinical Development of Combination Drug Products**

As typically observed for antisense oligonucleotides, monoclonal antibodies also display unique, species-specific profiles for pharmacologic activity. However, it is our understanding that the idiotype, control antibodies that are used to establish background levels for immunohistochemical staining studies have not been used to date in the clinic as control cohorts in clinical trials to support registration of these compounds.

In past interactions with the Agency regarding an antisense oligonucleotide combination product, we have received input that clinical trials may need to be conducted with a scrambled sequence to validate mechanism of action data observed in preclinical models. It is noted that scrambled or miss-sense oligonucleotides were not used in the clinical trials supporting the registration of the antisense drug Vitravene™ and were not required for the Phase 3 evaluation of the anticancer oligonucleotide Genasense (or for any other clinical programs with antisense oligonucleotides, to this author's knowledge). Further, such testing would not be of any therapeutic benefit to patients.

However, if the Agency requires that a scrambled oligonucleotide sequence be assessed in the clinic, such clinical trials would need to be supported by nonclinical toxicity studies of the exact scrambled sequence, which would obviously be very resource-consuming. For many antisense oligonucleotide programs, there is also currently a requirement to assess the nonclinical toxicity of animal-active analogues (*i.e.,* to address potential adverse effects associated with exaggerated pharmacologic activity). These animal-active analogues typically have a completely different nucleotide base sequence than the human drug, and, hence, they have no activity in humans. Therefore, it is reasonable to consider using the animal-active oligonucleotide(s) *in lieu*

of a scrambled sequence, as it fulfils the criteria of a structurally similar molecule with no expected antisense activity in humans. This strategy would obviate the need for dedicated nonclinical toxicity testing of a scrambled sequence to support a clinical study with such an entity, which would result in substantial sparing of animal use. Based on the assumption that combination antisense oligonucleotide products are captured within the scope of the current draft guidance, we recommend that this consideration be addressed in the guidance document, *i.e.,* that an animal-active analogue combination (for which toxicity testing has already been completed) can be used as a control to assess the mechanism of observed clinical activity.

Sincerely,

Jon Daniels, Ph.D., DABT
Director, Pharmaceutical & Healthcare Group